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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,779	06/29/2005	Kevin L. Rozwadowski	4810-69922-01	5541

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EXAMINER
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SHEN, WU CHENG WINSTON

ART UNIT	PAPER NUMBER
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1632

MAIL DATE	DELIVERY MODE
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08/26/2008

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<p align="center"><b>Advisory Action</b> <b>Before the Filing of an Appeal Brief</b></p>	<b>Application No.</b> 10/516,779	<b>Applicant(s)</b> ROZWADOWSKI ET AL.	
	<b>Examiner</b> WU-CHENG Winston SHEN	<b>Art Unit</b> 1632	

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 01 August 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☐ The period for reply expires \_\_\_\_\_ months from the mailing date of the final rejection.  
 b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on 24 January 2008. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

#### AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because  
 (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);  
 (b) ☐ They raise the issue of new matter (see NOTE below);  
 (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or  
 (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: See Continuation Sheet. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).  
 5. ☒ Applicant's reply has overcome the following rejection(s): Applicant's reply has not overcome any rejection of the record. See 3 and 11.  
 6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).  
 7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.  
 The status of the claim(s) is (or will be) as follows:  
 Claim(s) allowed: \_\_\_\_\_.  
 Claim(s) objected to: \_\_\_\_\_.  
 Claim(s) rejected: 1,3,4,6-13,16,17 and 20-28.  
 Claim(s) withdrawn from consideration: 2.

#### AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).  
 9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).  
 10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

#### REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.  
 12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). \_\_\_\_\_.  
 13. ☐ Other: \_\_\_\_\_.

/Thaian N. Ton/  
Primary Examiner, Art Unit 1632

Continuation of 3. NOTE: Applicant's response filed on 08/01/2008 addresses the issue of claim identifier documented on the "Notice of Non-Compliant Amendment" mailed on 07/02/2008. The Examiner acknowledges that the claim set filed on 08/01/2008 marks the status of claims 7-13 and 16-21 properly and is in compliance with 37 CFR 1.121. However, it is noted that Applicant does not address the issues documented on the Advisory Action mailed on 07/02/2008. Therefore, this advisory action reiterates Examiner's position below, which has been documented on the Advisory action mailed on 07/02/2008.

The proposed amended claim 6 reads as follows: The method of claim 1, wherein the gene targeting construct comprises an msr coding region encoding an RNA component of the gene targeting substrate called an msr element and an msd coding region encoding an a DNA component of the gene targeting substrate called an msd element". The claim amendments raise new issues that would require further consideration and/or search. The claim amendments, if entered, would necessitate a new rejection under 35 USC 112 second of the newly recited limitation "an msd coding region encoding a DNA component of the gene targeting substrate called an msd element". It is unclear how "an msd coding region", which is DNA as commonly accepted by the term "coding region", encodes a DNA..

Continuation of 11. does NOT place the application in condition for allowance because: Applicant's arguments have failed to overcome the rejection of claims 6, 8, 9, 10, 11, 12, and 24-28 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because Applicant's arguments rely on the proposed claim amendments, which have not been entered. The rejection is maintained of the record.

Applicant's arguments have failed to overcome the rejection of claims 1, 3, 4, 7, 10, 13, 16, 17, 20, 21, 22, and 23 under 35 U.S.C. 103(a) as being unpatentable over Conrad et al. (Conrad et al. U.S. Patent Application Publication No: 2003/0082800 A1, Publication date, May 1, 2003), priority to 10/091998) taken with Levin (Levin, A novel mechanism of self-primed reverse transcription defines a new family of retroelements. Mol Cell Biol. 15(6): 3310-7, 1995, cited previously) because Applicant's arguments have been fully considered and found not persuasive. The rejection is maintained of the record.

(i) Applicant argues that on page 3315 of Levin, second column, Levin goes to some length to describe the uncertainties associated with the putative self-priming mechanism described therein, including discussing the possibility that particular enzymatic activities might be required for that mechanism to operate. Given the relevant uncertainties, in the absence of an illustration that self-priming mechanisms are capable of mediating adequate reverse transcription for gene targeting, there is no basis in the cited art for one to expect that the putative mechanism of Levin could be used in gene targeting (See page 10 of response filed on 05/27/2008).

In response, Levin et al is not relied on for gene targeting nucleic acid, which is taught by Conrad et al. Levin is relied solely on the teachings that messenger RNA can self-prime reverse transcription in yeast cells (See page 7 of Final office action mailed on 07/24/2008), which reads on step (i) of claim 1, which recites the limitation "wherein the message RNA self-primers reverse transcription by a reverse transcriptase (RT) expressed by the host cell or the transformed progeny of the host cell". Claim 1 of instant application comprises multiple steps, which does not preclude the possibility that other enzymatic activities, including endonuclease, RNaseH may be involved in self-priming mechanism, as discussed by Levin on page 3315 right column. Furthermore, in contrast to Applicant's arguments, Levi does show the looped mRNA structure and DNA synthesis after priming (See page 7 of Final office action mailed on 07/24/2008 directing to Fig 1 of Levi).

(ii) Applicant argues that the self-priming mechanism of Levin is elucidated by showing that the sequences involved in self priming are sensitive to various mutations; there is accordingly no suggestion that the mechanism disclosed therein is sufficiently robust to tolerate manipulation for the purposes of generating an effective gene targeting vector. Also, the putative mechanism of Levin requires pairing between 3' and 5' sequences of an mRNA, suggesting that alternations in the intervening sequences might well have an effect on the efficiency of priming.

In response, Levin demonstrated that stable stem loop structure is required for reverse transcription by showing a compensatory mutation (i.e. changed a C:G base pair to a G:C base pair) can restore loop structure required for reverse transcription (See Fig. 1, Levin et al.). Moreover, in contrast to Applicant's arguments, Levin does not suggest that alternations in the intervening sequences between 5' and 3' of a given mRNA might have an effect on the efficiency of priming, rather Levin emphasizes that the formation of stem loop structure is critical for reverse transcription (See Fig. 2, Table 3, Levin)..